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Solventless Mechanochemistry Of *Bis*(Indolyl)Methanes

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ABSTRACT

Ball-milling technique as a solvent-free and an alternative green process was investigated for the eco-benign synthesis of *bis*(indolyl)-methanes (BIMs) from various aldehydes and selected ketones with indoles in high yields. The present methodology has several advantages such as simple procedure, good yields, mild conditions, and reduced environmental consequences. The silica gel acts both as a grinding medium and an acid catalyst. The utility of this technique was demonstrated by synthesizing library of 17 BIMs including two natural products trisindoline and tris(1H-indol-3-yl)methane.

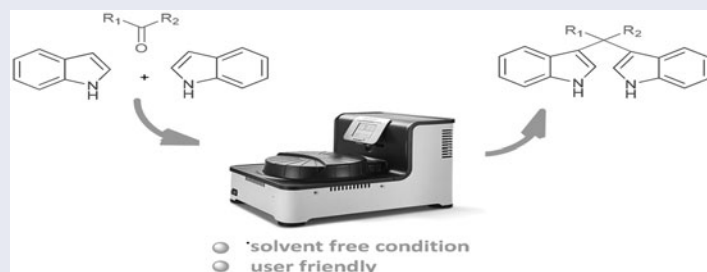
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Alkaloids; ball Milling; *bis*(indolyl)methanes; mechanochemistry; trisindoline


GRAPHICAL ABSTRACT



Introduction

To decrease the use of excess chemicals in routine chemical synthesis is of prime importance to a practicing synthetic chemist to reduce his/her contribution to global warming. The use of solvent-free conditions,^[1] green solvents,^[2] environment-friendly reagents, and catalysts^[3] are some of the means to achieve greenness in synthetic methodologies. Various non-classical energy sources such as ultrasound,^[4] microwave,^[5] infrared,^[6] LED lights^[7] are also included in green chemistry protocols. In recent times, ball-milling mechanochemistry, as an alternate green solvent-free method for organic transformations has opened a new vista of research.^[8] Many benefits are associated with mechanochemistry over solution based methods like time efficiency, environment friendliness and cost. Applications of mechanochemistry to a wide variety of organic reactions are explored including, olefin metathesis, coupling reactions and multistep synthesis.

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Indole, a nitrogen heterocycle is found in numerous natural products.^[9] BIMs also called as diindolylmethanes or diindo-3-yl-methanes are of interest because of their wide range of biological activities.^[10] They are useful in the treatment of irritable bowel, fibromyalgia, and fatigue.^[11] They also show inhibition of proliferation of estrogen-dependent as well as independent cancer cells.^[12] In nature, BIMs are found mainly in cruciferous plants and marine organism.^[9] Few selected natural BIMs are shown in [Figure 1](#). Arundine (**1**) was isolated from the roots of *Arundodonax*.^[13] Vibrindole A (**2**) was isolated from the marine bacterium *Vibrio parahaemolyticus*, associated with the toxic mucus of the boxfish *Ostracioncubicus* which exhibits antibacterial activity against *S. aureus* and *S. albus*.^[14] Streptindole (**3**), is a genotoxic metabolite of human intestinal bacteria *Streptococcus faecium* IB 37.^[15] Alkaloids arsindoline A (**7**) and B (**4**) were isolated from a marine bacterial strain CB101.^[16] 1,1,3-Tris(1*H*-indol-3-yl)butane (**5**) was isolated from the North sea bacterium *Vibrio parahaemolyticus* Bio249 along with Tris(1*H*-indol-3-yl)methane(**6**).^[17] Trisindoline (**8**) an antibiotic indole trimer was isolated from *Vibrio sp.* obtained from the marine sponge *Hyrtios altum*.^[18] Trisindoline (**8**) was also isolated from another marine bacterium *Vibrioparahaemolyticus* Bio249^[17] (North sea) and from terrestrial plant *Isatiscostate* which displays antibiotic property.^[19]

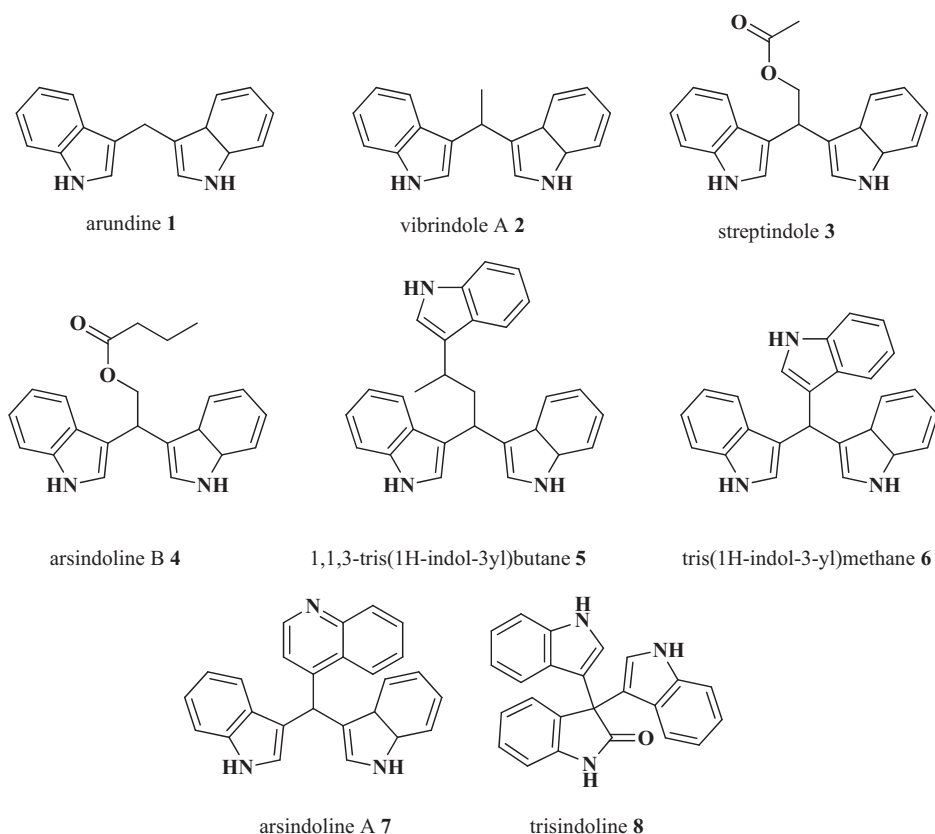


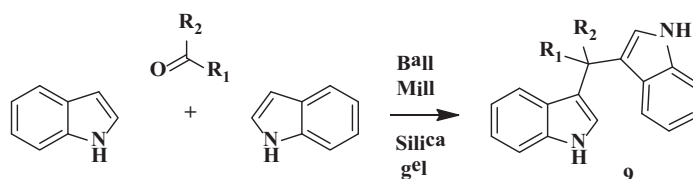
Figure 1. Selected naturally occurring BIMs.

BIMs are commonly synthesized from two molecules of indole and one molecule of carbonyl compounds. Various green protocols are reported for this three component condensation reaction.^[1-7] The other agents includes protic acids,^[20] Lewis acids such as TiO₂,^[21] CeCl₃,^[22] CuBr₂,^[23] ZrCl₄,^[24] lanthanide triflates,^[25] *N*-bromosuccinimide,^[26] KHSO₄,^[27] HY-zeolite,^[28] montmorillonite K-10,^[29] InCl₃,^[30] NaHSO₄/amberlyst,^[31] sulfamic acid,^[32] iron(III)(salen)Cl,^[33] ionic liquids^[34] and deep eutectic solvents.^[35] Synthesis of BIMs has also been established through hetero-Diels-Alder reactions.^[36] However, some of these methods have their limitations as the high cost of the reagents, limited substrate scope, harsh conditions, etc. Hence, there is a need to find alternative green methods.

In 2012, we had reported a catalyst-free and solvent-free method to synthesize BIMs without any promoters.^[1a] In this method, a mixture of indole and aldehydes were ground using mortar and pestle to obtain the products. However, the method has its limitation of non-uniform grinding, indefinite time, limited substrate scope, and scaling problems. These limitations can be overcome by using a ball-milling technique. Recently, Ranu et al.^[37] have developed an efficient procedure for transesterification using a ball mill in the absence of any solvent, acid/base or a metal catalyst. The reactions were carried out on the surface of basic alumina, which plays a dual role of a grinding auxiliary and a base. Hence, we envisaged that silica gel could play a similar role in the BIMs synthesis (Scheme 1).

Results and discussion

To begin with, we mixed 1.0 mmol of *o*-chorobenzaldehyde, 2.0 mmol of indole and added silica gel as supporting material to make the mass equal to 1.0 g. The mixture was then milled in a ball mill using 10 balls. The reaction was complete within 25 min. The product (**9a**, Fig. 2) was then obtained by filtration column using ethyl acetate: hexanes as eluent. The structure of the product was confirmed by its spectral data which matched perfectly with that reported in the literature.^[38] After the first success, the reaction was repeated with few more benzaldehydes possessing electron withdrawing groups (4-chloro, 2-nitro, 4-nitro, and 2-fluoro) (Fig. 2, **9b–e**). The reactions were found to complete with good yields in 20 min to 2.5 h. Next, we investigated the reaction with parent benzaldehyde, where the reaction was found to complete in 1.5 h. After the successful evaluation of parent benzaldehyde and aldehydes having electron withdrawing groups, further reactions were attempted with benzaldehydes having electron donating groups. 4-Methoxybenzaldehyde is known to give no product with hand grinding. Pleasingly, when the reaction was tried in a ball mill, after 10 h of grinding the product **9g** was obtained in 82%. The success of this prompted us to try the reaction on 3,4-



Scheme 1. General scheme for the synthesis of BIMs.

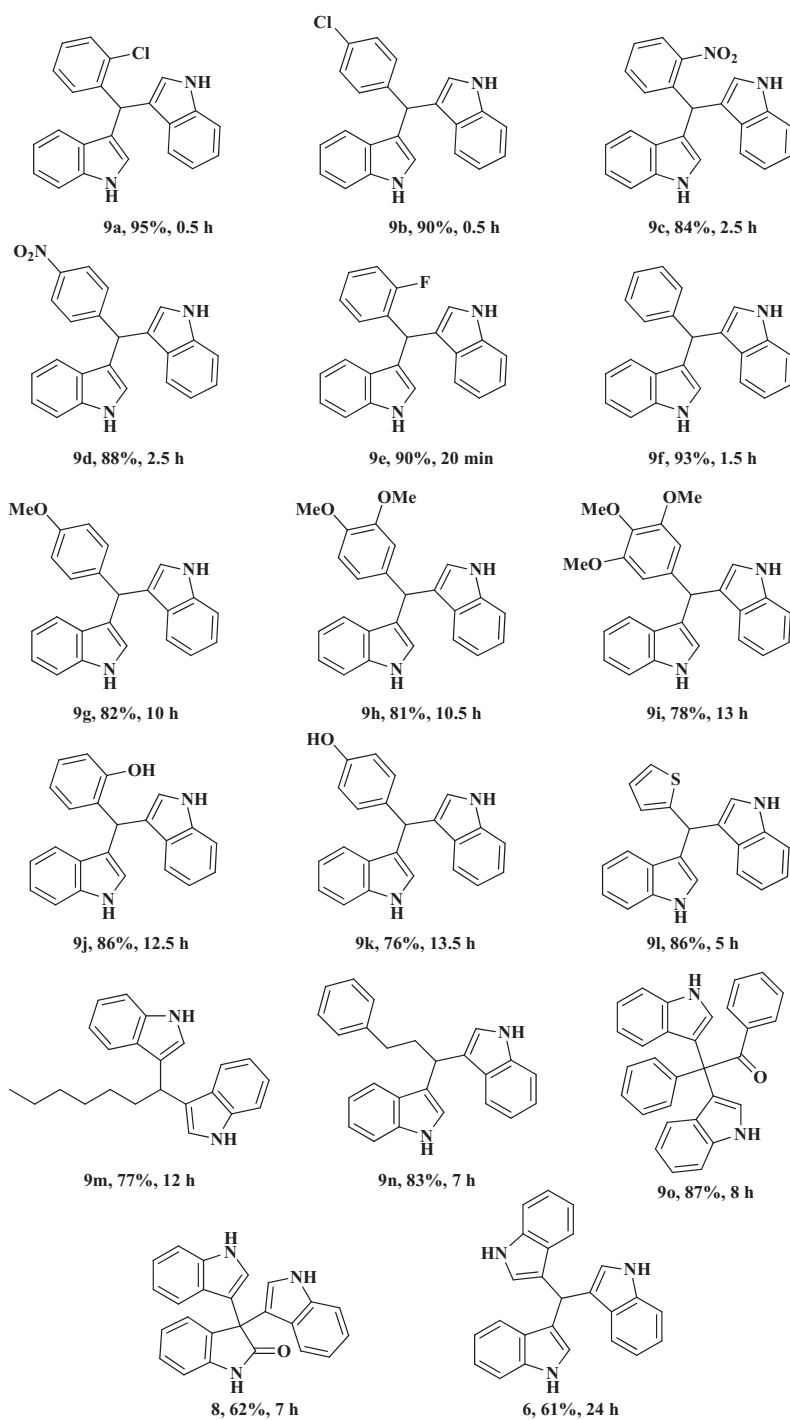
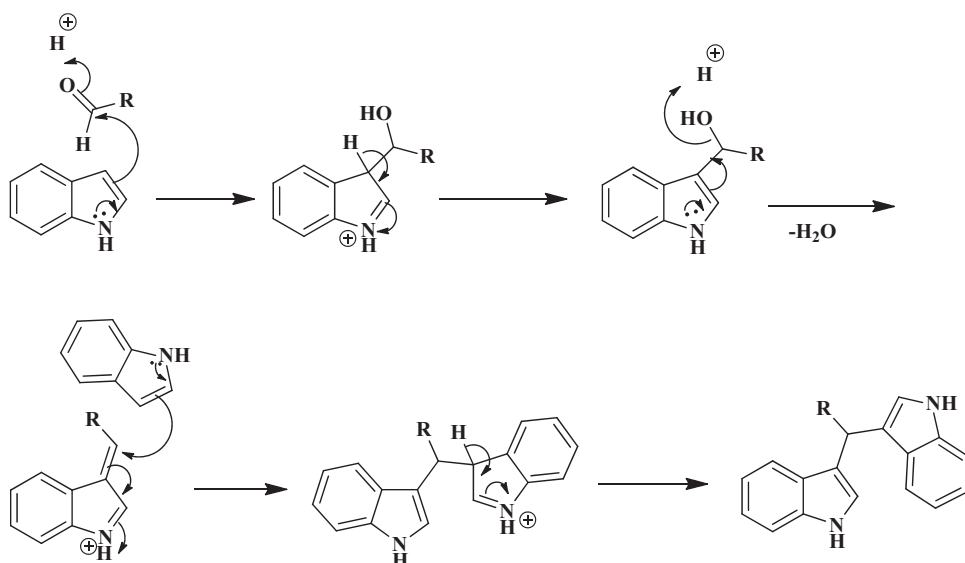


Figure 2. Synthesized BIMs.

dimethoxybenzaldehyde where the reaction gave the expected product **9h** in 81% in 10.5 h. Similarly, 3,4,5-trimethoxybenzaldehyde also gave the corresponding BIM product **9i** in 13 h. *o,p*-Hydroxybenzaldehydes reacted smoothly to give the corresponding



Scheme 2.. Probable mechanism for the formation of BIMs.

BIMs with 86% yields (Fig. 2, **9j,k**). The protocol also provided the BIM product with a heteroaldehyde (Fig. 2, **9l**). The BIM product with aliphatic aldehydes were also obtained in satisfactory yields (Fig 2, **9m,n**). Next, this strategy also facilitated the synthesis of natural product trisindoline (**8**). α -Ketoamide isatin smoothly reacted with indole to give the corresponding BIM in 62% yield (**8**, Fig. 2). The diketo compound benzil also reacted under the present conditions to give the condensed product (**9o**, Fig. 2). However, the unactivated ketones, acetophenone, and benzophenone failed to react. Gratifyingly, 3-formyl indole after 24 h rendered the natural product **6**.

The probable course of the reaction of indole with aldehyde or ketone proceeds through azafulvene intermediate which upon addition of the second mole of indole yields BIMs. The silica gel acts both as a grinding medium and an acid catalyst to deliver the products (Scheme 2).

Conclusion

We have successfully demonstrated the ball-milling technique as an efficient technique for the synthesis of BIMs using silica as a support material. The utility of this technique was demonstrated by synthesizing library of 17 BIMs including two natural products. The normally less reactive electron-rich aryl aldehydes, aliphatic aldehydes and selected ketones were found to be amenable for this technique.

Experimental

All the required solvents and chemicals were purchased from commercial suppliers and used without further purification. The reactions were carried out using the planetary ball milling machine (PULVERISETTE 7) marketed by FRITSCH and monitored using thin layer chromatography. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were

recorded on Bruker AVANCE III instrument. Chemical shifts are expressed in δ relative to tetramethylsilane (TMS). DEPT experiments were used to find the multiplicities of carbon signals. Coupling constants (J) are reported in Hertz (Hz).

Representative procedure for the synthesis of 3,3'-(2-fluorophenyl)methylene)bis(1H-indole) **9e**

To a mixture of 2-fluorobenzaldehyde (1 mmol) and indole (2 mmol) an appropriate amount of silica gel (60–120 mesh) was added to make the total mass equal to 1 g. This was then milled in a ball mill using 10 balls for 20 min. The reaction mass was then poured on a column of silica gel and purified using hexanes/ethyl acetate as an eluent to furnish the product **9c** as a red solid, 90%; mp 92–94 °C, lit³⁹ 94–95 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.48 (br, s, 2H), 7.31 (d, J = 8 Hz, 2H), 7.22 (d, J = 8 Hz, 2H), 7.11–7.05 (m, 4H), 7.00–6.86 (m, 4H), 6.51 (br, s, 2H), 6.13 (s, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 161.9, 159.4 (d, J = 244 Hz), 136.7, 131.0, 130.8, 130.42 (130.38), 127.9 (127.8), 126.9, 123.9 (123.9), 123.7, 122.0, 119.8, 119.3, 115.4 (115.2), 111.2, 32.5 (32.4, 31.00) ppm. MS (m/z): calculated for C₂₃H₁₆FN₂ [M - H]⁻ 339.1297; found 339.1298.

The characterization data for all the other BIMs could be found in the supporting information provided with this article.

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